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Is Cytomegalovirus Testing of Blood Products Still Needed for Hematopoietic Stem Cell Transplant Recipients in the Era of Universal Leukoreduction?

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A B S T R A C T

Hematopoietic stem cell transplantation (HSCT) recipients are a high-risk, immunocompromised group of patients who receive frequent transfusions after transplantation. Transfusion of cytomegalovirus (CMV)-negative blood products has long been the standard of care to prevent transfusion-transmitted CMV in this patient population. Leukoreduction of blood products before transfusion has been shown to significantly reduce the risk of transfusion-transmitted CMV. In the era of universal leukoreduction in Canada, the need for CMV testing of blood products remains unclear. We sought to identify whether there is a difference in transfusion-transmitted CMV viremia in patients receiving only leukoreduced versus CMV-negative and leukoreduced blood products in HSCT recipients. Patients who were CMV negative and received an allogeneic HSCT from a CMV-negative donor between October 1, 1999 and June 30, 2012 were included in the analysis. Transfusion data were collected from The Ottawa Hospital Blood Bank and Canadian Blood Services. CMV viremia was defined as PCR positivity. One hundred sixty-six patients were identified who met the inclusion criteria. Of these, 89 patients received an HSCT before January 2007, during the time when patients received leukoreduced and CMV-negative blood products. Seventy-seven patients received an HSCT after this time, receiving only leukoreduced blood products. The 2 groups did not differ in terms of age, gender, diagnosis, graft type, graft source, conditioning regimen, or ABO compatibility ($P > .05$). CMV viremia was detected in 3 patients who received CMV-negative leukoreduced blood products (3.37%) and in 1 patient who received only leukoreduced blood products (1.30%, $P = .6244$). Of the patients who developed CMV viremia, 2 developed suspected CMV disease. Both of these patients were transfused with CMV-negative blood products. Secondary outcomes, including total length of stay in hospital, admission to the intensive care unit, acute and chronic graft versus host disease, and 100-day nonrelapse mortality, did not differ between the groups. In the era of universal leukoreduction of blood products, this study demonstrates that testing for CMV-negative blood products is not needed for HSCT recipients.

INTRODUCTION

Transfusion practices over the years have drastically changed to improve the quality and safety of products transfused. One such change has been the implementation of universal leukocyte reduction of all transfused red cell and platelet products in Canada beginning in 1999. This was implemented after leukoreduction was shown in studies to decrease the incidence of febrile nonhemolytic transfusion reactions by approximately half, from .33% to .37% in red blood cell (RBC) [1-3] transfusion and from .18% to .19% in platelet [1,4,5] transfusions. Furthermore, multiple studies have shown that leukocyte reduction decreases the rate of alloimmune platelet refractoriness [6].

Cytomegalovirus (CMV) transmission is a recognized complication of blood transfusions. CMV is a DNA virus that, after primary infection, remains in a latent form. Sites of latency are believed to include bone marrow progenitor cells and monocytes. Prevalence of CMV antibodies in the general adult population ranges from 40% to 100% [7], with some studies showing a higher prevalence among men, people from a lower socioeconomic status, and at an increasing age [8]. In Canada, the seroprevalence has been estimated at 60% to 70% [8].One Canadian study showed that CMV seroprevalence among daycare workers was associated with increasing patient age, interaction with children, and low income birth country [9].

Transfusion-transmitted CMV infection in transfusion recipients who are immunocompetent is uncommon, reported to be about 1% [10]. This incidence is thought to be higher in immunocompromised patients, including hematopoietic stem cell transplantation (HSCT) recipients [11]. The most significant disease manifestations of CMV in HSCT recipients are pneumonia and gastrointestinal disease, both of which are associated with significant morbidity and mortality in these patients [9]. CMV pneumonia in HSCT recipients has been associated with mortality in 85% to 90% of these patients [12,13]. With pre-emptive treatment with antivirals, this has become much less common [14,15].

Efforts have been made to decrease the risk of CMV transmission via blood product transfusion in high-risk patients such as HSCT recipients. One landmark study in the 1980s identified that the use of CMV-seronegative blood

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products significantly reduced the absolute risk of CMV infection by 21% in CMV-seronegative HSCT recipients when compared with standard, non-leukoreduced blood product use [16]. The standard of care since then has been to provide CMV-seronegative blood products to HSCT recipients.

The introduction of universal leukoreduction of blood products has resulted in a move away from this standard in some transplant centers. In Canada, currently the practice is divided in that half of transplant centers continue to require CMV-negative blood products for allogeneic HSCT recipients (S. Couban, M. Seftel, R. Foley, D. Stewart, and J. Sepher, personal communication by Internet survey through the Canadian Blood and Marrow Transplant Group, June 2012). There have been conflicting reports as to whether leukoreduced blood products are as effective at preventing transfusion-transmitted CMV as CMV-negative products when transfusing high-risk patients. Bowden et al. [17] demonstrated through a randomized prospective study that bedside filtration of leukocytes, an older, arguably less effective, method of leukoreduction, was as effective as CMV-seronegative blood products in preventing transfusion-transmitted CMV infection in HSCT recipients. In contrast, a prospective cohort study found transfusion of each additional filtered RBC unit from CMV-positive blood donors was associated with a 32% increase in the odds of developing transfusion-transmitted CMV [18]. In addition to leukoreduction, PCR monitoring for CMV and effective pre-emptive therapy with ganciclovir make it more unclear if there remains a need to provide CMV-negative blood products to HSCT recipients. We sought to identify whether there is a difference in transfusion-transmitted CMV viremia and disease in patients receiving only leukoreduced versus CMV tested negative and leukoreduced blood products in HSCT recipients at The Ottawa Hospital.

METHODS

Patients and Transfusion Data

We performed an uncontrolled "before–after" study using prospectively collected institutional data. Patients included in the analysis were serologic CMV-negative adults aged 18 years or older who received an allogeneic HSCT from a CMV-negative donor at The Ottawa Hospital HSCT Program between October 1, 1999 and June 30, 2012. Patient demographics included age, gender, disease, graft type, graft source, related or unrelated match status, degree of HLA match, ABO blood group compatibility, and conditioning regimen. All patients provided consent for collection of relevant health information for clinical research. Data were analyzed in an anonymous fashion in accordance with approval of The Ottawa Hospital Research Ethics Board.

Transfusion data were collected from The Ottawa Hospital Blood Bank. CMV status of transfused units was obtained from Canadian Blood Services. As per Canadian Blood Services standards, all RBC and platelet products were leukoreduced at collection before component storage. The use of leukoreduced RBC and platelet products began at The Ottawa Hospital on September 3, 1999 (P. Lesley, Canadian Blood Services, personal communication, 2013). As of January 1, 2007, as per change in policy at The Ottawa Hospital, patients receiving an allogeneic HSCT received standard leukoreduced products that were not specifically tested for CMV. Hereafter throughout this study, patients who received only leukoreduced blood products are referred to as leukoreduced, whereas patients who received leukoreduced blood products that were tested to be CMV negative are referred to as CMV negative. All patients in this study received irradiated (25 Gy) blood products.

Clinical Outcomes

The primary outcome was CMV viremia, defined as PCR positivity, evaluated in all patients who met the above criteria. CMV testing was done on a weekly basis after neutrophil and platelet engraftment after transplantation until immune suppression was discontinued. CMV testing was performed using the Amplicor CMV monitoring assay (Roche Diagnostics, Branchburg, NJ). This assay has been used at our center since 1998. Amplicor is an automated PCR assay using an enzyme immunoassay detection system. The linear range of the assay is 400 to 100,000 copies per milliliter. The sensitivity and specificity of this Amplicor assay has previously been established as 96% and 98%, respectively [19]. CMV disease was defined as tissue biopsy–proven CMV or CMV seropositivity with signs and symptoms known to be associated with CMV, namely retinitis, ependymitis, hepatitis, esophagitis, colitis, and pneumonia [20].

Secondary outcomes were total length of stay in hospital; admission to the intensive care unit; time to neutrophil engraftment, defined as a neutrophil count $> .5 \times 10^9$/L for at least 3 days; time to platelet engraftment, defined as a platelet count $> 50 \times 10^9$/L with no platelet transfusions for 3 days; incidence of grades II to IV acute graft-versus-host disease (GVHD) at 100 days; incidence of chronic GVHD, reported for patients surviving at least 100 days; 100-day nonrelapse mortality, defined as death in the absence of underlying disease within the first 100 days; RBC transfusion requirements during the 30 days after the marrow infusion; and platelet transfusion requirements during the 30 days after marrow infusion. GVHD was graded using standard published criteria [21].

Statistical Analysis

Baseline characteristics were described using measures of central tendency and dispersion where appropriate. For the comparison of proportions, chi-square or Fisher's exact test were performed. Times to engraftment and transfusion requirements were analyzed using Student's *t*-test. Continuous variables were analyzed using Wilcoxon rank test. All statistical analyses were carried out using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

From October 1, 1999 to June 30, 2012, 166 patients were identified who met inclusion criteria. Eighty-nine patients received an HSCT before January 1, 2007, during the time when patients received leukoreduced and CMV-negative blood products. One hundred percent of patients in this cohort received CMV-negative blood products alone. Seventy-seven patients received an HSCT after this time, receiving only leukoreduced blood products.

The 2 groups did not differ in terms of age or gender (Table 1). There were no significant differences in diagnoses, graft type, graft source, conditioning regimen, or ABO compatibility between the 2 groups (Table 1).

There was no difference in the incidence of CMV viremia in those receiving CMV-negative versus leukoreduced blood products. CMV viremia was detected in 3 patients who received CMV-negative blood products (3.4; 95% confidence interval, .3% to 9.1%) and in 1 patient who received only leukoreduced blood products (1.3; 95% confidence interval, .7% to 9.5%; $P = .62$). Details of these 4 patients can be found in Table 2. All 4 patients received treatment with i.v. ganciclovir. Of the patients who developed CMV viremia, 2 developed suspected CMV disease. Both of these patients were transfused with CMV-negative blood products. One developed CMV viremia and acute respiratory failure requiring intensive care unit admission. This patient was concomitantly diagnosed with systemic *Aspergillus fumigatus* infection requiring antifungal therapy. The second patient also required admission to the intensive care unit for respiratory failure and was diagnosed with concomitant HHV-6 viremia. Both patients died of respiratory failure.

The mean length of stay for patients receiving CMV-negative versus leukoreduced only blood products was 41.5 and 46.8 days, respectively ($P = .47$). The proportion of patients who went to the intensive care unit was also not different in the 2 cohorts ($P = .10$). Time to neutrophil and platelet engraftment was not different between the 2 groups (Table 3, Figures 1 and 2). The incidences of overall (any grade) and severe (grades III to IV) acute GVHD were not different in the 2 groups ($P = .39$ and .13, respectively). The incidence of chronic GVHD was 22.5% in patients receiving CMV tested negative blood products versus 23.4% in patients receiving only leukoreduced blood products ($P = .52$). Overall

Table 1
Patient Characteristics

	CMV Negative (n = 89)		Leukoreduced (n = 77)		*P*
	n	%	n	%	
Gender (% female)	27	30.3	30	39.0	.24
Age (mean ± SD)	39.5 ± 13.4		43.5 ± 15.5		.07
Diagnosis					
ALL	12	13.5	10	13.0	.18
AML	19	21.4	27	35.1	
CML	14	15.7	2	2.6	
Hodgkin lymphoma	6	6.7	5	6.5	
Non-Hodgkin lymphoma	14	15.7	9	11.7	
MDS/MPN	9	10.1	10	13.0	
CLL	7	7.9	8	10.4	
Plasma cell disorders	2	2.3	2	2.6	
Other*	6	6.7	4	5.2	
Graft type					
PBSC	53	59.6	53	68.8	.21
BM	36	40.5	24	31.2	
Graft source					
Allo HLA match	46	51.7	30	39.0	.19
Allo HLA match unrelated	36	40.5	42	54.6	
Allo HLA mismatched	7	7.9	5	6.5	
Conditioning regimen					
Myeloablative	70	78.7	53	68.8	.21
Nonmyeloablative	19	21.4	24	31.2	
ABO mismatch	44	49.4	39	50.7	.88
30-Day transfusion needs (mean ± SD; units)					
SDP	9.6 ± 11.8		8.8 ± 10.8		.43
RDP	3.3 ± 15.8		.5 ± 2.6		.01
RBC	9.0 ± 10.6		7.2 ± 7.7		.23

ALL indicates acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; CLL, chronic lymphocytic leukemia; PBSC, peripheral blood stem cells; BM, bone marrow; SDP, single-donor platelets; RDP, random donor platelets.

* "Other" includes hemoglobinopathy, inherited disorders of metabolism, and nonhematologic malignancies.

survival was not different between the 2 groups ($P = .37$, Figure 3). The 100-day mortality for patients receiving CMV-negative blood products versus patients receiving only leukoreduced blood products was 22.5% and 14.7%, respectively ($P = .24$).

At 30 days, the number of packed RBC transfusions and single donor platelet units was not different ($P = .23$ and .43, respectively). There were, however, more transfusions of random donor platelets to patients receiving CMV-negative blood products versus those receiving leukoreduced-only transfusions (mean 3.3 versus .5 units, respectively; $P = .01$). Of the patients who received leukoreduced-only blood products, data were available on the CMV status of all units transfused until day 30 after HSCT for 63 patients (provided by Canadian Blood Services). The mean number of CMV-negative RBC units transfused was 6.4 ± 4.4, CMV-positive RBC units was 1.9 ± 1.4, CMV-negative platelet units was 3.7 ± 2.9, and CMV-positive platelet units was 4.1 ± 3.0. Patient D with CMV viremia (Table 2) who received leukoreduced-only blood products received 4 RBC units that were CMV negative, 2 RBC units that were CMV positive, 3 units of platelets that were CMV negative, and 11 units of platelets that were CMV positive within 30 days after HSCT.

DISCUSSION

Transfusion-transmitted CMV can be a potentially fatal consequence for HSCT recipients. Since the 1980s, CMV-seronegative transfusion products have been used in these patients to decrease CMV viremia and disease. It is unclear if this is still required in the era of universal leukoreduction of blood products in Canada. Our study demonstrated no difference in CMV viremia or disease in patients receiving CMV-negative leukoreduced versus leukoreduced-only blood products. This study suggests that in the age of universal leukoreduction in Canada, routine testing of blood products for CMV may not be warranted for HSCT recipients.

Our data are in accordance with reported results from other institutions. In a small study of 23 CMV-negative HSCT recipients from a CMV-negative donor, none of the patients developed anti-CMV antibodies after being transfused with CMV untested blood products, indicating that the risk of transfusion-transmitted CMV is close to zero with leukoreduction [22]. These data should be cautiously interpreted, however, because antibody formation in patients receiving an HSCT may be impaired due to immunosuppression. Although our incidence of CMV viremia was low with leukoreduction only (1.3%), the risk was still not zero. Although

Table 2
CMV-Positive Patients

Patient	HSCT Date	Transfusions	Time to CMV Detection*	Method of CMV Detection	CMV Disease	Outcome
A	Jan 2000	CMV negative	61	Blood - PCR	Pneumonitis	Respiratory failure, died day 190
B	Nov 2002	CMV negative	31	BAL - PCR	Pneumonitis	Respiratory failure, died day 35
C	Jul 2006	CMV negative	49	Blood - PCR	No	CMV negative after 3 wk of treatment
D	Jun 2007	Leukoreduced	32	Blood - PCR	No	CMV negative after 6 wk of treatment

BAL indicates bronchoalveolar lavage.

* Time to CMV detection reported in days after HSCT.

Table 3
Clinical Outcomes

	CMV Negative (n = 89)	Leukoreduced (n = 77)	*P*
Total LOS, d (mean ± SD)	41.5 ± 20.0	46.8 ± 32.0	.47
Patients who went to ICU, n (%)	15 (16.9)	21 (27.3)	.10
Days to neutrophil engraftment* (mean ± SD)	19.0 ± 5.9	19.3 ± 5.5	.65
Days to platelet engraftment* (mean ± SD)	32.5 ± 53.7	27.2 ± 22.9	.90
100-Day nonrelapse mortality, n (%)	13 (14.6)	9 (11.7)	.65
Acute GVHD (overall), n (%)	37 (41.6)	27 (35.1)	.39
Acute GVHD (severe), n (%)	9 (10.1)	14 (18.2)	.13
Chronic GVHD, n (%)	20 (22.5)	18 (23.4)	.52

LOS indicates length of stay; ICU, intensive care unit.
* Absolute neutrophil count >.5 × 10^9/L for at least 3 days; platelets >50 × 10^9/L with no platelet transfusions for at least 3 days.

it is possible that patients can develop CMV through means other than transfusion, these possibilities are less likely; therefore, we assume the transmission to be through transfusion. Seronegative donors still have the potential to pass CMV DNA to the transfusion recipient, especially in the window period after infection [23]. CMV testing in this circumstance will not recognize the donor as CMV positive because the antibody testing (which is standard practice for testing CMV in blood donors) will remain negative. This window period is believed to be days to weeks but has been reported to be as long as months [24]. This provides an explanation for the development of CMV viremia, albeit at a low incidence, even in patients receiving CMV-negative blood products. The inability of CMV serologic testing to detect window period donations provides further rationale for using standard leukoreduced blood products.

Similar to our study, CMV viremia in patients receiving leukoreduced blood products at the University of Michigan was not different in patients receiving CMV-negative versus CMV-untested transfusions [25]. In this study, however, most patients in the CMV-negative cohort received a mix of CMV-negative and CMV-untested blood products, making the results difficult to interpret. In our study, 100% of patients in the CMV-negative cohort received CMV-negative blood products.

Although transfusion-transmitted CMV was present in this study, the mortality related to CMV disease remained unclear. Two patients who were given CMV-negative and leukoreduced blood products developed presumed CMV disease based on CMV viremia and pulmonary symptoms thought to be related to CMV pneumonitis. In both cases, however, concomitant infections (*A. fumigatus* in 1 and HHV-6 in the other) may have contributed to the mortality observed in these patients. CMV disease was not observed in our cohort of patients receiving CMV-untested leukoreduced blood products after 2007.

Despite the small number of patients in this study, the results have important clinical implications. In a transplant center that has performed 491 allogeneic HSCTs during the time course of this study, 166 (33.8%) were CMV-negative donor and recipient pairs. The transfusion-transmitted CMV incidence was very low in patients receiving leukoreduced CMV-negative (3.4%) and -untested (1.3%) blood products, with no significant difference in nonrelapse mortality at 100 days after HSCT. In a moderately sized transplant center, the clinical impact of CMV testing was therefore negligible in the era of universal leukoreduction. If we estimate the incidence of CMV viremia to be 3% with CMV-untested blood products as observed in this study, a very large sample size would be needed in a randomized prospective trial to show a clinically relevant risk reduction. With an already low incidence of CMV viremia, this would be impractical and unlikely to change clinical practice.

There are limitations to our study that warrant attention, predominantly associated with our retrospective design. We attempted to minimize selection bias by including all

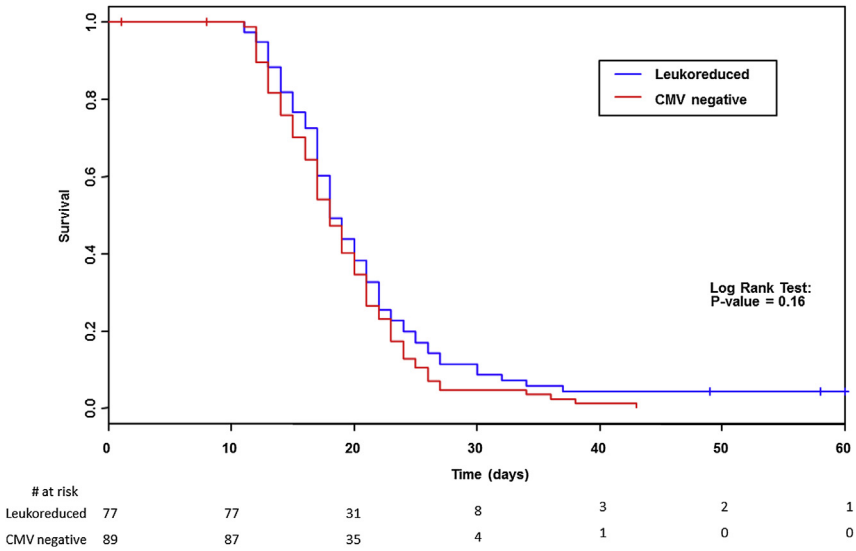

Figure 1. Neutrophil engraftment by transfusion group.

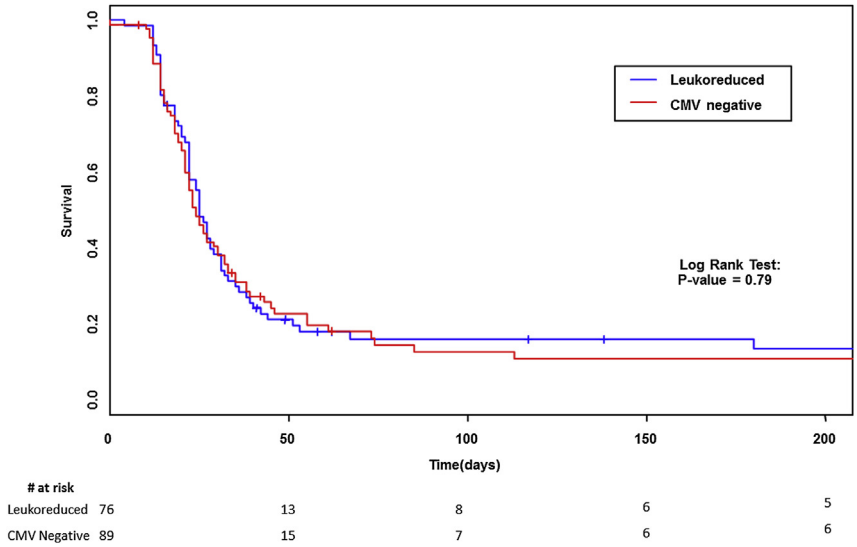

Figure 2. Platelet engraftment by transfusion group.

consecutive patients with CMV-negative patient–donor HSCTs at The Ottawa Hospital. Second, although our study provides acute and chronic GVHD rates, the types and duration of GVHD treatment were not captured. This could impact the risk of CMV viremia because patients receiving immunosuppressive treatment for GVHD would be at higher risk of CMV disease. Third, trends in transplantation practice may have influenced our results. General supportive care measures did not change during the study period. The practice of universal prophylaxis with acyclovir and the antivirals used for the treatment of CMV were unchanged throughout the study period, as was the policy of high-resolution HLA testing. Although no significant difference in baseline characteristics was identified, a higher proportion of patients with chronic myelogenous leukemia received CMV-negative leukoreduced blood products (15.7% versus 2.6%). This is due to the increasing use of tyrosine kinase inhibitors, eliminating the need for transplant in many of these patients.

The median age was nonsignificantly higher in the CMV-negative leukocyte reduced cohort, as was the use of peripheral blood as a stem cell source. Furthermore, random donor platelets were more commonly used in the earlier cohort of patients receiving leukoreduced CMV-negative blood products. This likely reflects a change in practice rather than a significant difference in the patient populations. Single-donor apheresis platelets have always been preferred to random donor platelets in HSCT recipients and have become more available in recent years. Our transplant center has also moved toward a more conservative threshold for platelet transfusions. These factors together contributed to the observation that patients receiving leukoreduced-only blood products received fewer random platelet donor transfusions. Despite these limitations, to our knowledge, this is the largest study to compare allogeneic HSCT recipients receiving CMV-negative versus CMV-untested blood products in the era of universal leukoreduction. A large randomized control trial would be impractical and would not

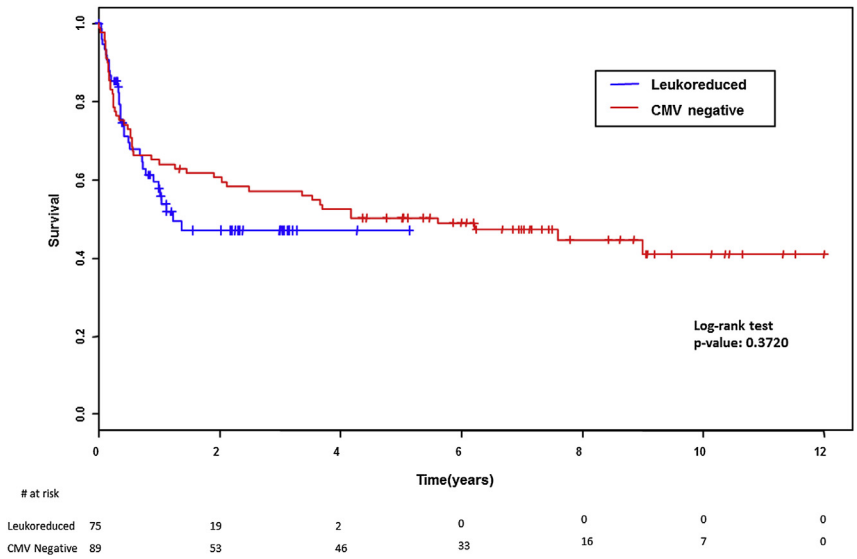

Figure 3. Overall survival by transfusion group.

likely show a difference in CMV viremia or disease that would impact clinical outcomes.

In the era of universal leukoreduction of blood products, this study demonstrates that testing for CMV-negative blood products is not needed in HSCT recipients. Our findings have implications for national health care resource utilization. Currently, about 47% of donors at Canadian Blood Services are individually tested for CMV. The cost of the medical supplies alone for CMV testing at Canadian Blood Services is estimated to be 745,000 CAD per year (G. Balkar, Canadian Blood Services, personal communication, 2013). HSCT recipients consume a significant number of blood products, and eliminating the need for CMV testing for this patient population nationwide could result in substantial cost savings.

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REFERENCES

1. Yazer MH, Podlosky L, Clarke G, Nahirniak SM. The effect of prestorage WBC reduction on the rates of febrile nonhemolytic transfusion reactions to platelet concentrates and RBC. *Transfusion*. 2004;44:10-15.
2. King KE, Shirey RS, Thoman SK, et al. Universal leukoreduction decreases the incidence of febrile nonhemolytic transfusion reactions to RBCs. *Transfusion*. 2004;44:25-29.
3. Vamvakas EC. Meta-analysis of randomized controlled trials of the efficacy of white cell reduction in preventing- alloimmunization and refractoriness to random-donor platelet transfusions. *Transfus Med Rev*. 1998;12:258-270.
4. Paglino JC, Pomper GJ, Fisch GS, et al. Reduction of febrile but not allergic reactions to RBCs and platelets after conversion to universal prestorage leukoreduction. *Transfusion*. 2004;44:16-24.
5. Heddle NM, Blajchman MA, Meyer RM, et al. A randomized controlled trial comparing the frequency of acute reactions to plasma-removed platelets and prestorage WBC-reduced platelets. *Transfusion*. 2002;42:556-566.
6. Blajchman MA. The clinical benefits of the leukoreduction of blood products. *J Trauma*. 2006;60(6 Suppl.):S83-S90.
7. de Jong MD, Galasso GJ, Gazzard B, et al. Summary of the II International Symposium on Cytomegalovirus. *Antiviral Res*. 1998;39:141-162.
8. Cannon MJ, Schmid DS, Hyde TB. Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection. *Rev Med Virol*. 2010;20:202-213.
9. Joseph SA, Beliveau C, Muecke CJ, et al. Risk factors for cytomegalovirus seropositivity in a population of day care educators in Montréal, Canada. *Occup Med (Lond)*. 2005;55:564-567.
10. Preiksaitis JK, Brown L, McKenzie M. The risk of cytomegalovirus infection in seronegative transfusion recipients not receiving exogenous immunosuppression. *J Infect Dis*. 1988;157:523-529.
11. Vancíková Z, Dvorák P. Cytomegalovirus infection in immunocompetent and immunocompromised individuals—a review. *Curr Drug Targets Immune Endocr Metabol Disord*. 2001;1:179-187.
12. Enright H, Haake R, Weisdorf D, et al. Cytomegalovirus pneumonia after bone marrow transplantation. Risk factors and response to therapy. *Transplantation*. 1993;55:1339-1346.
13. Meyers JD, Flournoy N, Thomas ED. Risk factors for cytomegalovirus infection after human marrow transplantation. *J Infect Dis*. 1986;153:478-488.
14. Saleh AJ, Al Mohareb F, Al Rabiah F, et al. High efficacy and low toxicity of short-course oral valganciclovir as pre-emptive therapy for hematopoietic stem cell transplant cytomegalovirus infection. *Hematol Oncol Stem Cell Ther*. 2010;3:116-120.
15. Goodrich JM, Bowden RA, Fisher L, et al. Ganciclovir prophylaxis to prevent cytomegalovirus disease after allogeneic marrow transplant. *Ann Intern Med*. 1993;118:173-178.
16. Bowden RA, Sayers M, Flournoy N, et al. Cytomegalovirus immune globulin and seronegative blood products to prevent primary cytomegalovirus infection after marrow transplantation. *N Engl J Med*. 1986;314:1006-1010.
17. Bowden RA, Slichter SJ, Sayers M, et al. A comparison of filtered leukocyte-reduced and cytomegalovirus (CMV) seronegative blood products for the prevention of transfusion-associated CMV infection after marrow transplant. *Blood*. 1995;86:3598-3603.
18. Nichols WG, Price TH, Gooley T, et al. Transfusion-transmitted cytomegalovirus infection after receipt of leukoreduced blood products. *Blood*. 2003;101:4195-4200.
19. Diaz-Mitoma F, Leger C, Miller H, et al. Comparison of DNA amplification, mRNA amplification, and DNA hybridization techniques for detection of cytomegalovirus in bone marrow transplant recipients. *J Clin Microbiol*. 2003;41:5159-5166.
20. Boeckh M, Geballe AP. Cytomegalovirus: pathogen, paradigm, and puzzle. *J Clin Invest*. 2011;121:1673-1680.
21. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease. I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant*. 2005;11:945-956.
22. Thiele T, Krüger W, Zimmermann K, et al. Transmission of cytomegalovirus (CMV) infection by leukoreduced blood products not tested for CMV antibodies: a single-center prospective study in high-risk patients undergoing allogeneic hematopoietic stem cell transplantation (CME). *Transfusion*. 2011;51:2620-2626.
23. Ziemann M, Juhl D, Görg S, Hennig H. The impact of donor cytomegalovirus DNA on transfusion strategies for at-risk patients. *Transfusion*. 2013;53:2189-2199.
24. Ziemann M, Unmack A, Steppat D, et al. The natural course of primary cytomegalovirus infection in blood donors. *Vox Sang*. 2010;99:24-33.
25. Nash T, Hoffmann S, Butch S, et al. Safety of leukoreduced, cytomegalovirus (CMV)-untested components in CMV-negative allogeneic human progenitor cell transplant recipients. *Transfusion*. 2012;52:2270-2272.